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EXAMINER

O FARRELL, THOMAS JOHN

ART UNIT

PAPER NUMBER

1634

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Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/664,234

Applicant(s)

RUAN ET AL.

Examiner

Thomas J. O'Farrell

Art Unit

1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 09 December 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-52 is/are pending in the application.
- 4a) Of the above claim(s) 1-24 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 25-52 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 09/07/2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date 3/11/04, 2/14/05
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

## **DETAILED ACTION**

### ***Election/Restrictions***

1. Applicant's election without traverse of group 2, claims 25-41 with species election of Mmel in claim 35, in the reply filed on 12/09/2005 is acknowledged. New claims 44-52 have been added to group 2 as requested by applicant. With respect to claim 35, restriction enzyme species BsmFI and Mmel were examined.

The requirement is still deemed proper and is therefore made FINAL

2. Claims 25-41 and 44-52 are currently under consideration. An action on the merits follows. Claims 1-24, 42, and 43 are withdrawn from consideration as being drawn to non elected inventions.

### ***Specification***

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see page 15 of specification). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

### ***Double Patenting***

Art Unit: 1634

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 26-30, 33-39, and 44-52 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3-6, 8, 10, 11, 13, and 21 of copending Application No. 11045468.

Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1, 3-6, 8, 10, 11, 13, and 21 of the '468 application recite methods of creating ditags by linking the 3' and 5' termini of nucleic acids that were inserted into a vector and cleaved from with restriction enzymes, sequencing the ditags, mapping the ditag sequence to the genome. The term "ditag" of claims 1, 3-6, 8, 10, 11, 13, and 21 of the '468 application is defined on page 4 of the '468 application specification to encompass polynucleotides comprising 34-38 nucleotides (instant claim

38). Therefore, claims 1, 3-6, 8, 10, 11, 13, and 21 of the '468 application are coextensive in scope with instant pending claims 26-30, 33-39, and 44-52.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

6. Claims 25-28, 30, 31, 33-35, and 37-42 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 5 of copending Application No. 11145005.

Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-3 and 5 of the '005 application recite methods of linking a first linked tag and a second linked tag, interpreted as 5' and 3' termini, that were flanked by adaptors, to form a ditag, further encompassing forming concatemers of ditags, detecting gene expression with ditags, and comparing the sequence of the ditags to sequences of databases of known genes. Therefore, claims 1-3 and 5 of the '005 application are coextensive in scope with instant pending claims 25-28, 30, 31, 33-35, and 37-42.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

### ***Claim Rejections - 35 USC § 112***

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

Art Unit: 1634

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 25-41 and 44-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The instant claims recite the phrase "3' terminus" or "5' terminus". It is unclear whether "3' or 5' terminus" refers to the 1<sup>st</sup> nucleotide on the 3' or 5' end of the polynucleotide or whether it includes any nucleotide that has another nucleotide 5' to the 3' terminus or 3' to the 5' terminus.

Claims 45-47 and 52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 45 and 52 recite "...wherein each adaptor includes at least one restriction site and wherein each adapter includes at least a first restriction site which is an symmetric restriction site and at least a second restriction site". It is unclear how each adapter can have one restriction site but have a first restriction site and a second restriction site.

### ***Claim Rejections - 35 USC § 102***

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 25-35, 38, and 43-45 are rejected under 35 U.S.C. 102(b) as being anticipated by Kinzler et al. (herein referred to as Kinzler, US 6383743, 07/2002).

The examiner interprets 5' or 3' terminus of a polynucleotide as any fragment or whole piece of a polynucleotide that contains the actual 5' or 3' terminus of the polynucleotide.

Kinzler teaches a method of creating ditags where cDNA is cleaved by an anchoring enzyme (AE), fragments containing the 3' or 5' ends of the cDNA are isolated and ligated with linkers, the fragments are cleaved again by an asymmetric restriction enzyme (TE) with a recognition site within the linker, and the resulting fragments are ligated back together and can be cleaved again by the anchoring enzyme for concatenation (claims 27, 30 and 34; see Figure 1 and column 5, lines 55-65 of Kinzler). Kinzler teaches that the anchor enzyme will not likely cut cDNAs of less than 256 bp (see column 4, lines 57-61 of Kinzler). In the method described above, Figure 1A of Kinzler teaches that the polynucleotides can have adaptors on both sides which can be a primer adaptor with AE and TE recognition sites and a biotin on the other side (claim 26), and after cleavage with the TE enzyme, the 3' and 5' ends of each strand of the DNA double helix are isolated into the primer adapter (such as Primer A) (see Figure 1A and B of Kinzler). Kinzler teaches that subsequent ligation will ligate fragments from different genes together but will also ligate the 3' and 5' termini of the complimentary strands of the same polynucleotide together flanked by two adapters (claims 25 and 26). Kinzler teaches that the polynucleotide formed after ligation is a polynucleotide

flanked with two adapters which have asymmetric recognition sites, that can be type II restriction endonuclease sites, which can be cleaved again to link the 5' and 3' termini again (claims 33 and 34; see Figure 1V of Kinzler, and column 5, lines 56-64 of Kinzler). Kinzler teaches these asymmetric recognition sites can be for the enzyme BsmFI (claim 35; see column 5, lines 62-65 of Kinzler). Kinzler teaches that concatemers formed by the ditags of the above method can consist of about 2-200 ditags (claim 28; see column 7, lines 19 and 20 of Kinzler). Kinzler teaches that the ditags can be inserted into vectors (claim 29; see column 7, lines 30-33, 44 and 45 of Kinzler). Kinzler teaches that the ditags can be sequenced and used to detect gene expression (claim 31; see column 12, lines 38-67, and Figure 2 of Kinzler). Kinzler teaches that the sequence of the ditag can be matched to sequences of a database of genomic sequences to identify known sequences that match the ditag sequence (claim 32; see column 9, lines 25-34 and 58 of Kinzler). Kinzler teaches that ditags can be from about 12-60 bp (claim 38; see column 6, lines 24-25 of Kinzler).

10. Claims 25-30, 33-35, 38, and 44-48 rejected under 35 U.S.C. 102(b) as being anticipated by Hodgson (herein referred to as Hodgson, US 2002/0025561 A1, 02/28/02).

Hodgson teaches a method of assembling DNA molecules which includes isolating the 3' and 5' terminus of a polynucleotide that has been phosphorylated, interpreted as an adapter, into a vector that has two adapters having type IIS restriction endonuclease sites, including *Sap1*, cutting the DNA out of the vector with the



Art Unit: 1634

appropriate type IIS restriction endonuclease, and ligating the DNA with other DNAs into the vector to link the 5' and 3' terminus of the original polynucleotide (claims 25-27, 29, 33- 35, and 44, see Figure 1, and para 0026 of Hodgson). Hodgson teaches that up to 32 DNA fragments prepared as above from *SapI* digestion can be concatemerized into a vector (claim 28; para 0031, lines 8-10 of Hodgson). Hodgson teaches that the polynucleotides that are to be assembled can be genomic DNA, introns, and exons (claim 30; see all of para 0056 of Hodgson). Hodgson teaches that the original polynucleotides that are to be assembled can be 100-300 bp (claim 38; see para 0040, lines 11-12 of Hodgson). Hodgson teaches a vector, pWB, for inserting the polynucleotides to be assembled that contains a multiple cloning site having regions interpreted to be adapters to flank an insert where the adapters have *SapI* sites and other restriction enzyme sites, *NruI* in one adapter and *TfiI* in the other adapter, that are not also in the vector backbone (claims 45-48; see Figure 2 of Hodgson).

### ***Claim Rejections - 35 USC § 103***

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claim 35 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kinzler in view of the New England Biolabs 2000/2001 Catalog.

Kinzler teaches a method of creating ditags where cDNA is cleaved by an anchoring enzyme (AE), fragments containing the 3' or 5' ends of the cDNA are isolated and ligated with linkers, the fragments are cleaved again by an asymmetric restriction enzyme (TE) with a recognition site within the linker, and the resulting fragments are ligated back together and can be cleaved again by the anchoring enzyme for concatenation (see Figure 1 and column 5, lines 55-65 of Kinzler). In the method described above, Figure 1A of Kinzler teaches that the polynucleotides can have adaptors on both sides which can be a primer adaptor with AE and TE recognition sites and a biotin on the other side, and after cleavage with the TE enzyme, the 3' and 5' ends of each strand of the DNA double helix are isolated into the primer adapter (such as Primer A) (see Figure 1A and B of Kinzler). Kinzler teaches that subsequent ligation

will ligate fragments from different genes together but will also ligate the 3' and 5' termini of the complimentary strands of the same polynucleotide together flanked by two adapters. Kinzler teaches that the polynucleotide formed after ligation is a polynucleotide flanked with two adapters which have asymmetric recognition sites, that can be type II restriction endonuclease sites, which can be cleaved again to link the 5' and 3' termini again (see Figure 1B of Kinzler, and column 5, lines 56-64 of Kinzler). Kinzler teaches that the type II restriction endonucleases cleave at a defined distance of up to 20 bp away from their asymmetric recognition sites and that these enzymes will be known in the art (see column 5, lines 59-65 of Kinzler).

Kinzler does not teach a method of ditag construction *specifically where the type II restriction endonuclease used is Mmel*. However, page 196 of the New England Biolabs 2000/2001 Catalog teaches that Mmel is an asymmetric restriction enzyme that cleaves 18-20 bp away from its recognition site. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use Mmel as a type II restriction endonuclease in the method of ditag construction taught by Kinzler in view of the teachings of the New England Biolabs 2000/2001 Catalog. The ordinary artisan would expect to have success and be motivated to use Mmel as a type II restriction endonuclease in the method of ditag construction taught by Kinzler because Kinzler teaches that type II restriction endonucleases cleave at a defined distance of up to 20 bp away from their asymmetric recognition sites and New England Biolabs 2000/2001 Catalog teaches that Mmel is an asymmetric restriction enzyme that cleaves 18-20 bp away from its recognition site.

14. Claim 36 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kinzler in view of Belfort et al. (Belfort, 1997, Nucleic Acid Research, vol. 25, pages 3379-3388).

Kinzler teaches a method of creating ditags where cDNA is cleaved by an anchoring enzyme (AE), fragments containing the 3' or 5' ends of the cDNA are isolated and ligated with linkers, the fragments are cleaved again by an asymmetric restriction enzyme (TE) with a recognition site within the linker, and the resulting fragments are ligated back together and can be cleaved again by the anchoring enzyme for concatenation (see Figure 1 and column 5, lines 55-65 of Kinzler). In the method described above, Figure 1A of Kinzler teaches that the polynucleotides can have adaptors on both sides which can be a primer adaptor with AE and TE recognition sites and a biotin on the other side, and after cleavage with the TE enzyme, the 3' and 5' ends of each strand of the DNA double helix are isolated into the primer adapter (such as Primer A) (see Figure 1A and B of Kinzler). Kinzler teaches that subsequent ligation will ligate fragments from different genes together but will also ligate the 3' and 5' termini of the complimentary strands of the same polynucleotide together flanked by two adapters. Kinzler teaches that the polynucleotide formed after ligation is a polynucleotide flanked with two adapters which have asymmetric recognition sites, that can be type II restriction endonuclease sites, which can be cleaved again to link the 5' and 3' termini again (see Figure 1B of Kinzler, and column 5, lines 56-64 of Kinzler).

Kinzler does not teach a method of preparing ditags *specifically where the ditag is flanked with adapters containing homing endonuclease asymmetric restriction sites*. However, Kinzler teaches an embodiment whereby the anchoring endonuclease used in the above method of ditag construction rarely cuts cDNA such that few or no cDNA representing abundant transcripts are cleaved (see column 5, lines 24-28 of Kinzler). Belfort teaches that homing restriction enzymes are rare cutting enzymes with asymmetric restriction sites and include I-CeuI, PI-SceI, PI-PspI, and I-SceI (see abstract, page 3379, column 2, para 2, lines 7-10; and Table 2 of Belfort). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use homing restriction enzymes, including I-CeuI, PI-SceI, PI-PspI, and I-SceI, in the adapters flanking the ditags taught by Kinzler in view of the teachings of Belfort. Because Kinzler teaches an embodiment whereby the anchoring endonuclease used in the above method of ditag construction rarely cuts cDNA such that few or no cDNA representing abundant transcripts are cleaved and Belfort teaches that homing restriction enzymes are rare cutting enzymes with asymmetric restriction sites, the ordinary artisan would have been motivated to use homing restriction enzymes, including I-CeuI, PI-SceI, PI-PspI, and I-SceI, to optimize the method of ditag construction taught by Kinzler.

15. Claims 39-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kinzler in view of Saha et al. (herein referred to as Saha, 2002, Nature Biotechnology, vol. 19, pages 508-512).

Kinzler teaches a method of creating ditags where cDNA is cleaved by an anchoring enzyme (AE), fragments containing the 3' or 5' ends of the cDNA are isolated and ligated with linkers, the fragments are cleaved again by an asymmetric restriction enzyme (TE) with a recognition site within the linker, and the resulting fragments are ligated back together and can be cleaved again by the anchoring enzyme for concatenation (see Figure 1 and column 5, lines 55-65 of Kinzler). Kinzler teaches that the anchor enzyme will not likely cut cDNAs of less than 256 bp (see column 4, lines 57-61 of Kinzler). In the method described above, Figure 1A of Kinzler teaches that the polynucleotides can have adaptors on both sides which can be a primer adaptor with AE and TE recognition sites and a biotin on the other side, and after cleavage with the TE enzyme, the 3' and 5' ends of each strand of the DNA double helix are isolated into the primer adapter (such as Primer A) (see Figure 1A and B of Kinzler). Kinzler teaches that subsequent ligation will ligate fragments from different genes together but will also ligate the 3' and 5' termini of the complimentary strands of the same polynucleotide together flanked by two adapters.

Kinzler does not teach a method of ditag construction and analysis further *specifically comprising mapping each of the two tags of the ditag on the genome; and further defining the structural region of the corresponding gene on the genome map (claim 39); or comparing the ditag with a genome map or a database; detecting matching 5' or 3' termini on the genome map but detecting no match on one or more gene database, further recovering the newly discovered gene (claims 40 and 41); or sequencing a ditag from a full length cDNA library and recovering the full-length cDNA*

*corresponding to the ditag (claim 42).* However, Saha teaches that ditags from a cDNA library can be matched to genomic sequence which allows precise localization of tags in the genome and that the comparison of tag locations with positions of previously annotated genes can provide expression evidence for predicted genes, and identify novel internal exons and previously uncharacterized genes (claim 39; see Figure 1 and page 511, column 2, para 2, lines 15-18 of Saha). Saha teaches that after mapping ditags to a genome map, potentially undiscovered genes can be identified by selecting ditags that do not match known genes of a database (claim 40; see page 509, column 2, all of para 2 and 3, and page 510, column 1, all of para 1 of Saha). Saha teaches that this method of ditag analysis can only identify a portion of a transcribed gene and different approaches such as RT-PCR and RACE are required to obtain full-length gene sequences from a cDNA library (claims 41 and 42; see page 510, column 2, all of para 1 of Saha). Saha teaches that systematic large-scale analysis of the genome using LongSAGE with ditags will be complementary to other approaches of gene identification (see page 510, column 2, para 3, lines 1-3 of Saha). Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to further use the ditags taught by Kinzler to map each of the two tags of the ditag on the genome; and further define the structural region of the corresponding gene on the genome map (claim 39); or compare the ditag with a genome map or a database; detect matching 5' or 3' termini on the genome map but no match on one or more gene database, and further recover the newly discovered gene (claims 40 and 41); or sequence a ditag from a full length cDNA library and recover the full-length cDNA

corresponding to the ditag (claim 42) in view of the teachings of Saha. The ordinary artisan would have been motivated to further use the ditags taught by Kinzler to map each of the two tags of the ditag on the genome; and further define the structural region of the corresponding gene on the genome map; or compare the ditag with a genome map or a database; detect matching 5' or 3' termini on the genome map but no match on one or more gene database, and further recover the newly discovered gene; or sequence a ditag from a full length cDNA library and recover the full-length cDNA corresponding to the ditag because Saha teaches that matching ditags from a cDNA library to genomic sequences allows *precise* localization of tags in the genome and that the comparison of tag locations with positions of previously annotated genes can provide expression evidence for predicted genes, and identify novel internal exons and previously uncharacterized genes, and Saha teaches that potentially undiscovered genes can be identified by selecting ditags that match to the genome map but do not match known genes of a database and provides methods to obtain full-length sequences of such new genes from a cDNA library as Saha teaches that longSAGE can only identify portions of transcribed genes.

16. Claims 46-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kinzler in view of the New England Biolabs 2000/2001 Catalog.

Kinzler teaches a method of creating ditags where cDNA is cleaved by an anchoring enzyme (AE), fragments containing the 3' or 5' ends of the cDNA are isolated and ligated with linkers, the fragments are cleaved again by an asymmetric restriction



Art Unit: 1634

enzyme (TE) with a recognition site within the linker, and the resulting fragments are ligated back together and can be cleaved again by the anchoring enzyme for concatenation (see Figure 1 and column 5, lines 55-65 of Kinzler). Kinzler teaches that the anchor enzyme will not likely cut cDNAs of less than 256 bp (see column 4, lines 57-61 of Kinzler). In the method described above, Figure 1A of Kinzler teaches that the polynucleotides can have adaptors on both sides which can be a primer adaptor with AE and TE recognition sites and a biotin on the other side (claim 26), and after cleavage with the TE enzyme, the 3' and 5' ends of each strand of the DNA double helix are isolated into the primer adapter (such as Primer A) (see Figure 1A and B of Kinzler). Kinzler teaches that subsequent ligation will ligate fragments from different genes together but will also ligate the 3' and 5' termini of the complimentary strands of the same polynucleotide together flanked by two adapters. Kinzler teaches that the polynucleotide formed after ligation is a polynucleotide flanked with two adapters which have asymmetric recognition sites, that can be type II restriction endonuclease sites, which can be cleaved again to link the 5' and 3' termini again (see Figure 1V of Kinzler, and column 5, lines 56-64 of Kinzler). Kinzler teaches that the ditags can be inserted into vectors (see column 7, lines 30-33, 44 and 45 of Kinzler). Kinzler teaches that the type II restriction endonucleases cleave at a defined distance of up to 20 bp away from their asymmetric recognition sites and that these enzymes will be known in the art (see column 5, lines 59-65 of Kinzler).

Kinzler does not teach ditags flanked by adapters with asymmetric and second restriction sites inserted into vectors *specifically where the vector backbone does not*

*comprise the restriction sites of the adapters* (claims 46-49). However, one of ordinary skill in the art would realize that having recognition sites for the asymmetric and second enzymes in the backbone of the vector would significantly compromise the efficiency of ligating the ditags into the vector as more vector fragments would need to be isolated and included in the ligation reaction. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of ditag construction taught by Kinzler, where the ditags flanked by adapters with asymmetric and second restriction sites inserted into vectors, specifically are inserted into vectors where the vector backbone does not comprise the restriction sites of the adapters in view of the teachings of Kinzler. The ordinary artisan would have been motivated to improve the method of ditag construction in view of Kinzler where the ditags flanked by adapters with asymmetric and second restriction sites inserted into vectors, specifically are inserted into vectors where the vector backbone does not comprise the restriction sites of the adapters, because one of ordinary skill in the art would realize that having recognition sites for the asymmetric and second enzymes in the backbone of the vector would significantly compromise the efficiency of ligating the ditags into the vector as more vector fragments would need to be isolated and included in the ligation reaction.

Kinzler does not teach a method of ditag construction where the ditags flanked by adapters with asymmetric and second restriction sites inserted into vectors *specifically are inserted into vectors where the vector backbone does not comprise Mmel sites of the adapters* (claim 49). However, page 196 of the New England Biolabs

Art Unit: 1634

2000/2001 Catalog teaches that Mmel is an asymmetric restriction enzyme that cleaves 18-20 bp away from its recognition site. Therefore, it would have been further prima facie obvious to one of ordinary skill in the art at the time the invention was made to use Mmel as a type II restriction endonuclease in the method of ditag construction taught by Kinzler in view of the teachings of the New England Biolabs 2000/2001 Catalog. The ordinary artisan would expect to have success and be motivated to use Mmel as a type II restriction endonuclease in the method of ditag construction taught by Kinzler because Kinzler teaches that type II restriction endonucleases cleave at a defined distance of up to 20 bp away from their asymmetric recognition sites and New England Biolabs 2000/2001 Catalog teaches that Mmel is an asymmetric restriction enzyme that cleaves 18-20 bp away from its recognition site.

17. Claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hodgson.

Hodgson teaches a method of assembling DNA molecules which includes isolating the 3' and 5' terminus of a polynucleotide that has been phosphorylated, interpreted as an adapter, into a vector that has two adapters having type IIS restriction endonuclease sites, including *Sap1*, cutting the DNA out of the vector with the appropriate type IIS restriction endonuclease, and ligating the DNA with other DNAs into the vector to link the 5' and 3' terminus of the original polynucleotide (claims 26; see Figure 1, and para 0026 of Hodgson).

Hodgson does not a method of ligating the 3' and 5' termini of a polynucleotide where the polynucleotide is *specifically a cDNA molecule*. However, Hodgson teaches that several types of polynucleotides can be assembled by the method of Hodgson including exons (see all of para 0056 of Hodgson). Therefore, because one of ordinary skill in the art would readily recognize that full-length cDNA can be conveniently used to represent the exon of a 1 exon gene, it would have been further prima facie obvious to one of ordinary skill in the art at the time the invention was made to use cDNAs in the method of assembling DNA molecules taught by Hodgson in view of the teachings of Hodgson. The ordinary artisan would expect to have success and be motivated to use cDNAs for assembling in the method taught by Hodgson because Hodgson teaches that several types of polynucleotides can be assembled by the method of Hodgson including exons and the ordinary artisan would readily recognize that full-length cDNA can be conveniently used to represent the exon of a 1 exon gene.

18. Claim 49 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hodgson in view of Tucholski et al. (herein referred to as Tucholski, 1995, Gene, vol. 157, pages 87-92).

Hodgson teaches a method of assembling DNA molecules which includes isolating the 3' and 5' terminus of a polynucleotide that has been phosphorylated, interpreted as an adapter, into a vector that has two adapters having type IIS restriction endonuclease sites, including *Sap1*, cutting the DNA out of the vector with the appropriate type IIS restriction endonuclease, and ligating the DNA with other DNAs into

Art Unit: 1634

the vector to link the 5' and 3' terminus of the original polynucleotide (claim 29; see Figure 1, and para 0026 of Hodgson). Hodgson teaches a vector, pWB, for inserting the polynucleotides to be assembled that contains a multiple cloning site having regions interpreted to be adapters to flank an insert where the adapters have SapI sites and other restriction enzyme sites, NruI in one adapter and TfiI in the other, that are not also in the vector backbone (claim 48; see Figure 2 of Hodgson).

Hodgson does not teach a method of assembling DNA molecules *specifically where the adapters used comprise MmeI sites*. However, Hodgson teaches that appropriate class IIS restriction enzymes can be used in the adapters of the vector to release the DNA fragments (see para 0026, lines 6-12 of Hodgson). Tucholski teaches that MmeI is a class IIS restriction enzyme capable of cutting 20/18 nucleotides away from its asymmetric recognitions sequence (see abstract of Tucholski). Therefore, it would have been further prima facie obvious to one of ordinary skill in the art at the time the invention was made to use other class IIS restriction enzyme sites, including MmeI, in the adapters of the vectors taught in the method of DNA assembly taught by Hodgson in view of the teachings of Tucholski. The ordinary artisan would have been motivated to use other class IIS restriction enzyme sites, including MmeI, in the adapters of the vectors taught in the method of DNA assembly taught by Hodgson because Hodgson teaches that appropriate class IIS restriction enzymes can be used in the adapters of the vector to release the DNA fragments and Tucholski teaches that MmeI is a class IIS restriction enzyme capable of cutting 20/18 nucleotides away from its asymmetric recognitions sequence.

19. Claims 50-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hodgson in view of Tucholski, further in view of GenBank accession number X65305.2 (herein referred to as GenBank accession number X65305.2, 01/2000).

Hodgson teaches a method of assembling DNA molecules which includes isolating the 3' and 5' terminus of a polynucleotide that has been phosphorylated, interpreted as an adapter, into a vector that has two adapters having type IIS restriction endonuclease sites, including *Sap*1, cutting the DNA out of the vector with the appropriate type IIS restriction endonuclease, and ligating the DNA with other DNAs into the vector to link the 5' and 3' terminus of the original polynucleotide (claim 29; see Figure 1, and para 0026 of Hodgson). Hodgson teaches a vector, pWB, for inserting the polynucleotides to be assembled that contains a multiple cloning site having regions interpreted to be adapters to flank an insert where the adapters have *Sap*I sites and other restriction enzyme sites, *Nru*I in one adapter and *Tfi*I in the other, that are not also in the vector backbone, and a Lac operator (see Figure 2 of Hodgson).

Hodgson does not teach a vector for assembling DNA molecules *specifically comprising SEQ ID NO:18* (claims 50-52). However, Hodgson teaches that appropriate class IIS restriction enzymes can be used in the adapters of the vector to release the DNA fragments (see para 0026, lines 6-12 of Hodgson). Tucholski teaches that *Mme*I is a class IIS restriction enzyme capable of cutting 20/18 nucleotides away from its asymmetric recognition sequence (see abstract of Tucholski). Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was

made to use other class IIS restriction enzyme sites, including Mmel, in the adapters of the vectors taught in the method of DNA assembly taught by Hodgson in view of the teachings of Tucholski. The ordinary artisan would have been motivated to use other class IIS restriction enzyme sites, including Mmel, in the adapters of the vectors taught in the method of DNA assembly taught by Hodgson because Hodgson teaches that appropriate class IIS restriction enzymes can be used in the adapters of the vector to release the DNA fragments and Tucholski teaches that Mmel is a class IIS restriction enzyme capable of cutting 20/18 nucleotides away from its asymmetric recognitions sequence.

Hodgson in view of Tucholski do not teach a vector for assembling DNA molecules *specifically comprising SEQ ID NO:18*. However, GenBank accession number X65305.2 teaches the sequence of pGEM-4Z, which is the backbone of the vector used for SEQ ID NO:18, and that pGEM-4Z has a multiple cloning site and a lac operator like pWB taught by Hodgson (see GenBank accession number X65305.2 and result #24 of search of SEQ ID NO:18 in GenEmbl database). Therefore, it would have been further prima facie obvious to one of ordinary skill in the art at the time the invention was made to use other vectors containing Mmel sites and other second restriction sites in the adapters, such as the vector of SEQ ID NO:18, in the method of assembly of DNA molecules taught by Hodgson in view of the teachings of Tucholski and GenBank accession number X65305.2. The ordinary artisan would have expected to have success and been motivated to use other vectors containing Mmel sites and other second restriction sites in the adapters, such as the vector of SEQ ID NO:18, in

Art Unit: 1634

the method of assembly of DNA molecules taught by Hodgson because Hodgson teaches that appropriate class IIS restriction enzymes can be used in the adapters of the vector to release the DNA fragments and Tucholski teaches that Mmel is a class IIS restriction enzyme capable of cutting 20/18 nucleotides away from its asymmetric recognitions sequence and GenBank accession number X65305.2 teaches the vector pGEM-4Z which contains a multiple cloning site and a lac operator like that of pWB taught by Hodgson, which is the backbone of the vector used for SEQ ID NO:18, and can be used to make a vector of similar function of pWB.

### ***Conclusion***

20. No claims are allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thomas O'Farrell whose telephone number is (571) 272-8782. The examiner can normally be reached Monday-Friday from 8:30 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.



Art Unit: 1634

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